**IN THE ABSTRACT**

Please enter the abstract submitted with the January 22 amendment.

REMARKS

1. 37 CFR §1.98(a)(1) does not require the use of "PTO-1449" to list patents, publications or other information being submitted for consideration by the PTO. It merely requires a "list" which provides the information set forth in §1.98(b). The use of form PTO-1449 for this purpose is entirely discretionary.

That said, Applicants are puzzled by the reference to an information disclosure statement filed "January 22, 1998". An IDS was filed on October 10, 1995, and acknowledged in the Office action of September 16, 1996.

Perhaps the Examiner is construing the amendment of January 22, 1998 as an IDS. The following items were enclosed with the amendment: Abstract of the Disclosure; Copy of the '809 patent; Fuh, et al. (1992); Lowman, et al. (1991); Fuh and Wells (1995); WO97/11178; Grossman (1994); Blaese (1995); Crystal (1995); Watahiki, et al. (1989); Cunningham and Wells (1989); Cunningham, et al. (1989); and Cunningham, et al. (1990).

Certain of these references were already of record:

Watahiki, et al. (1989): reference BY, sheet 3/6

Cunningham and Wells (1989): reference BP, sheet 3/6

Cunningham et al. (1989): reference BI, sheet 3/6

The others are not prior art, since Applicants earliest U.S. filing date was October 12, 1989, and the other references were published in 1990 or thereafter. In addition, they are cited in support of patentability.

Nonetheless, a PTO-1449 listing these other references (except for the '809 patent) is enclosed, with the understanding that, since they were cited and copies provided already, no charge will attach.

2. The present paper directs entry of the previously submitted abstract. The amendments discussed in section 8 of the

office action have been redirected to the proper location in the specification.

3. The insertion of certain text at page 7, line 31 has been challenged as the addition of "new matter", contrary to 35 USC §132.

At page 1, lines 5-6, the instant application incorporates by reference Ser. No. 08/313,505, filed September 26, 1994. The inserted text appears at page 4, last paragraph of the '505 application. It is clearly not a violation of 35 USC §132 to transfer text from the referenced application into the referencing application.

4. The rejections of method-of-use claims 46-60 (section 12) and method-of-making claim 61 (section 13) are moot as these claims have been canceled without prejudice or disclaimer.

5. The rejection (section 14, page 9) of claim 64 is moot as this claim has been canceled without prejudice or disclaimer.

6. The new indefiniteness rejection of claims reciting a percentage identity (section 15) is respectfully traversed.

At page 12, lines 6-10, Applicants make reference to the use of the "Micro-Genie" program for secondary structure prediction. Any person skilled in the art would have recognized that this was a general sequence analysis program, and, in the absence of instructions to the contrary, would have used if for any other sequence analysis, including sequence alignment, required by the specification and claims.

The "Micro-Genie" program (see User Manual December 1998, section 8.3, copy enclosed) offered two methods for sequence alignment: alignment by identity (option I) and alignment by similarity (option S).

In option I, the sequences were aligned, with gapping allowed, to maximize the quantity S=M-G-N, where M is the number of matches, G is the number of gaps, and N is the number of residues contained in the gaps. (This is equivalent to a scoring matrix with +1 for each match and 0 for each mismatch, with a gap

open penalty of -2 for the first null and a gap extension penalty of -1 for each additional null.)

In option S, the sequence are aligned by another algorithm "which is described by M. Dayhoff et al. in the Atlas of Protein Structure". While the exact literature citation is not given, a review of the Atlas for the period preceding the first U.S. filing reveals several Dayhoff publications in the Atlas, the most recent being Dayhoff, et al., "Model of Evolutionary Change in Proteins", 5 (Suppl:3):345-52 (1978) and "Matrices for Detecting Distant Relationships", 5 (Suppl:3):353-58 (1978) (copies enclosed).

Dayhoff converted the log odds matrices of Figures 84 and 85 into scoring matrices by adding a bias of 6 or 60, respectively (in Fig. 84, the original log odds elements were multiplied by 10, and in Fig. 85, by 100, before rounding off, hence the 10-fold difference in bias). He then normally imposed a length-independent break (gap) penalty of 6 for use with the matrix of Fig. 84 and 60 with the matrix of Fig. 85.

The MicroGenie program, in similarity mode, does not allow the user to control the choice of scoring matrix, bias, or break penalty. While we believe that these were the matrix of Dayhoff Fig. 84, with a bias of 6 and 9 break penalty of 6, the ultimate and completely definite standard is the program itself. It is also evident from Fig. 6 in Dayhoff, et al., Meth. Enzymol., 91:524-45 (1983) (copy enclosed) that Dayhoff's ALIGN program does not directly penalize end gaps, since it only penalized 7 breaks, and with the end gap, there would have been 8. We assume that the same is true of the MicroGenie software. Applicants no longer have a working copy of this software.

While the user manual does not point this out, Merrifield, "MicroGenie:Homology Searches", Chap. 19 in Meth. Mol. Biol., vol. 24:Computer Analysis of Sequence Data, Part I (Griffin and Griffin, eds., 1994) (copy enclosed), at page 249, section 3.2.4, step 7 state that alignment by similarity is the default.

Therefore, there is no ambiguity as to how the sequences are to be aligned, they are aligned by similarity according to the Dayhoff method implemented in the MicroGenie program, which is believed to be the Fig. 84 (PAM 250) scoring matrix with a bias of 6 and a break penalty of 6, with end gaps ignored.

With regard to the method of then calculating the percentage identity, given the above alignment, a person skilled in the art would interpret language of the form "50% identical to reference sequence R" (cp. spec., page 14, lines 19-24 and page 18, lines 6-12) to mean that one aligns the query sequence with the reference sequence, and then states the number of matches as a percentage of the length of the reference sequence.

The PTO has conceded the synonymity of "percentage homology" and "percentage identity" in the art (see slides shown at the recent PTO "open house").

In the examples of DNA alignments given on page 10, if the reference sequence were the "acgtac", the "left" alignment would produce a 67% identity and the "right" alignment would produce a 33% identity. Microgenie aligns DNA only by the identity method, for which the "left" alignment would score 4-2-1=1 and the "right" alignment would score 2-0-0=2 (since end gaps are not counted). So the alignment of these DNAs by MicroGenie would result unambiguously in a conclusion that the query sequence was 33% homologous with the reference sequence "acgtac". (If the reference sequence were the "acac", then the value would be 50%.)

7. Claims 29-33 have been rejected because they allegedly do not "contain sufficient structural elements in order to provide the claimed function". In essence, these claims combine a minimum percentage sequence identity with an activity requirement. The only restriction on <u>which</u> AAs are mutated <u>how</u> comes from the functional limitation. In contrast, claim 10 limits the mutation on a position-by-position basis.

The Examiner does not dispute that the PTO has allowed claims of this type in the past, but urges that any past conduct of the PTO is irrelevant, citing <u>In re Hutchison</u>, 69 USPQ 138

(CPA 1946). Apparently, Hutchison was allowed certain claims already, but the Court declined to compare the claims in dispute with those previously allowed.

Thus, the Examiner relies on a case, over 50 years old and preceding the 1952 Patent Act, which relates to the issue of whether inconsistency with a single prior patent is relevant. At pages 19-20, applicants cited 13 prior patents with the questioned claim format. In Andrew Corp. v Gabriel Electronics, Inc., 6 USPQ2d 2010 (Fed. Cir. 1988), the Federal Circuit Court of Appeals upheld the definiteness of "substantially equal", pointing out that the "criticized words are ubiquitous in patent claims" and "have been accepted in patent examination and upheld by the courts." And see also Ex parte Brian, 118 USPQ 242, 245 (POBA 1958) ("fingerprint" claim reciting IR absorption spectrum is definite "since the claims under consideration are similar to those in the ["numerous"] patents ["dealing with the subject matter involved in the present case"]").

With regard to the use of the activity limitation to avoid reading on structural embodiments, we cited Mark, which the Examiner distinguishes because it only contemplates mutation of cysteine residues.

We have reviewed the claims upheld in Ex parte Mark and it does not appear that they in fact require that the mutations be limited to the cysteine residues of the native protein, only that at least one of the differences between the mutein and the native protein be the replacement of a nonessential cysteine of the native protein.

Even if the Mark claims were so limited, it does not seem to be a great jump from determining which cysteine residues of a given protein are essential to activity to determining which residues of any kind are essential, in view of the disclosure of alanine-scanning mutagenesis at page 17, lines 7-15. Bovine GH, for example, has four cysteines out of 191 amino acids. Testing all positions for essentiality would therefore be just about 50 times the work of just testing the cysteines. Cunningham (1989)

tested positions 7-19, 54-74 and 167-191 of hGH, a total of 62 positions (positions 13 and 17 already being alanine). Thus, one-third of the work was done already.

In any event, as stated by Trial Judge Brown in General Electric Co. v. United States, 206 USPQ 260, 283-4 (Ct. Claims Trial Div. 1979), "the law does not require all of the claims to recite each and every element necessary to the operation of the invention... were this not the case, the claims would be prolix to the point of obscuring the inventive concept to which the claims are directed. It is the function of the specification, not the claims, to set forth sufficient detailed information to enable one skilled in the art to make and use the invention."

The Examiner is of the opinion that "one of ordinary skill in the art would not reasonably expect a protein which is only 50% identical to the native protein to be able to functionally bind a receptor or retain any biological activity". However, the percentage identity between hGH and bGH is only 66% (see page 14, line 21). The percentage identity of fin whale GH with human GH is only 68%, see Tsubokau and Kawauchi, Int. J. Peptide Protein Res., 25; 297-304 (1985).

The amino acid sequence homology (identity) of human GH with various fish growth hormones is reported to be as follows:

| Fish | Pctg. | Citation |
|---|---|---|
| Chum Salmon | 35 | Sekine, et al., Proc. Nat. Acad. Sci. (USA), 82:4306-10 (1985) |
| Tuna | 37 | Sato, et al., Biochem. Biophys. Acta, 949:35-42 (1988) |
| Yellowtail | 34 | Watahiki; et al., Gen. & Compar. Endocrinol., 70:401-6 (1988) |
| Rainbow Trout | 35% | Agellon and Chen, DNA, 5:463-71 (1986) |
| Caho Salmon | (1) | Nicoll, et al., Gen. & Compar. Endocrinol., 68:387-99 (1987) |
| Sea Bream | 33% | Momota, et al., Nucleic Acids Res., 16:3107 (1988) |

| | | |
|---|---|---|
| Eel | (2) | Yamaguchi, et al., Gen. & Compar. Endocrinol., 66:447-53 (1987) |

(1) Not stated, but coho salmon differs at only six residues from chum salmon.

(2) Not stated, but see their Fig. 5 for an alignment, and note that eel GH is said to have 48% identity with salmon GH, 56% with chicken GH, and 54% with bovine GH.

Duck GH has 56% homology with human GH, and 40% with salmon GH. See Chen, et al., Biochem. Biophys. Acta, 949:247-51 (1988).

Since all of these hormones have GH activity, it is plain that Applicants' "50% identity" limitation is in fact a conservative one, and the concept of "substantial homology" could readily reach at least as low as 33% identity (sea bream GH vs. human GH).

As stated on page 18, lines 22-24, Gill, et al., Bio/Technology, 3:643 (1985) reported that recombinant chicken and bovine GHs accelerate growth in juvenile pacific salmon.

The Examiner also states that the claims encompass deletion of as much as half of the protein and that there is no art of record to support the position that 50% of the GH molecule could be deleted and function as a receptor antagonist."

As disclosed on page 2, lines 22-29, the fragment bGH (96-133) has been reported to have receptor-binding and biological activity. Since bGH is 191 a.a., that fragment is 38/191, or 19.8%, of the full-length protein. Paladini, et al., CRC Critical Reviews in Biochemistry, 15:25-56 (19__) (copy enclosed) indicates that bGH 96-133 has about 5% of the effect of the native hormone in the tibial width increase assay (see Table 2), and that (Cam)-hGH 1-134 had a relative effect of 10-20% (Id.). The latter fragment is 134/191, or 70%, of the full-length protein. A 50% fragment would score somewhere between 5 and 20%, e.g., 10%.

There have been no studies of fragments of hGH G120X or bGH 119X. However, it is assumed that if a fragment of the

vertebrate GH promotes growth, the corresponding G119/G120 mutant will inhibit growth.

Even if the Examiner could fairly question the effect of deleting 50% of the molecule, per claim 29, other rejected claims require retention of a larger portion of the molecule, namely, 66% (claim 30), 80% (claim 31), or 90% (claim 32). See also new claim 65.

8. The Examiner objects to our "exclusionary proviso" as lacking basis in the original disclosure, citing Ex parte Grasselli (1983). However, In re Johnson, 194 USPQ 187 (CCPA 1977) held that one may excise prior art from the claim and still satisfy the written description requirement, regardless of whether there was literal basis for the negative limitation. Grasselli did not identify which cases were cited by applicants, or explain how they were distinguished. Therefore, we do not know if the Grasselli Board were even aware of In re Johnson, let alone distinguished it. Plainly, if Grasselli and Johnson are in direct conflict, Johnson must be followed, as the CCPA has appellate review authority over the Board.

Applicants also wish to point out that the very proviso questioned here was accepted by the PTO in a sibling application 08/486,794, which was allowed on November 5, 1997. The proviso in that case was added by a 1.312(a) amendment filed November 26, 1997, and the amendment in question was entered on March 24, 1998 in a paper signed by Stephen Walsh, Supervisory Patent Examiner, Art Unit 1646.

We have also presented an alternative, but narrower, claim, which does not resort to this proviso.

With the mutation G120L, Cunningham, et al. simultaneously introduced the mutations Y111V, L113I, K115E, D116Q, E118K, E119R, Q122E, T123G, G126L, R127I and E129S.

The G120L mutation satisfies clause (I) of claim 49. With regard to the other mutations, Applicants have compared these

mutations to the table of vertebrate growth hormones set forth by Harvey, et al. (Exhibit C to the October 23, 1996 amendment in 08/488,164).

If the alignment set forth in Harvey Fig. 1 is taken at face value, then we find the following divergences at each of the positions noted above:

| Mutation | mammal GH | bird GH | amphibian, reptile GH | fish GH |
|---|---|---|---|---|
| Y111V | none | F | none | S, T, F |
| **L113I** | K | K | K, R | K, R |
| K115E | R | none | R | S, A, E, R |
| **D116Q** | none | none | Y | E |
| E118K | none | none | D | K, R, N, E |
| E119K | none | none | none | M, T, V, K |
| **Q122E** | L | none | H | H, L, S, N, G, V, F |
| **T123G** | A | none | I | L, K, M, I, V, Y, E, A |
| G126L | Q R | R | R | R, T, E, K, M |
| R127I | E | E | E | A, T, G, V, D, E |
| E129S | none | none | D | Q, L, V, G |

The four boldfaced Cunningham mutations are conservative substitutions.

The underlined divergences represent nonconservative substitutions for the wild-type hGH residue. Thus, limitation (B)(II)(b)(i) would allow any nonconservative substitution at

each of the listed residues, including of course the mutation set forth by Cunningham.

New claim 66 requires that the first and second reference vertebrate growth hormones both be mammalian growth hormones. As a result, certain of the nonconservative mutations (Y111V, D116Q, E118K, E119K, E129S) incorporated into Cunningham's "hPRL111-129" mutant which otherwise would be within clause (B)(iI)(b)(i) (because of variation among vertebrate GHs) move outside that clause (because of the more limited variation among mammalian GHs). Therefore, absent evidence that they would satisfy clause (B)(II)(B)(ii), this requirement appears to be sufficient to distinguish Cunningham. Hence, new claim 66 lacks the challenged proviso.

By a similar argument, claims 25 and 26 distinguish "hPRL111-129" without the need for the "Cunningham" proviso, and hence claim 25 has been rewritten in independent form, without that proviso, as new claim 66.

Likewise, claim 13 could be rewritten in independent form without the "Cunningham" proviso.

Respectfully submitted,

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Enclosure
-Micro-Genie User Manual sec. 8.3
-Dayhoff (1978) (2 articles)
-Merrifield (1994)
-references cited on pp. 9-10 (except Gill, et al. 1985)

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